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#18 Nora 6/24/02

Attorney's Docket No. 35052/204373(5052-53) PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	et al.	Confirmation No.:	7095
Appl No.:	09/689,430	Group Art Unit:	1632
Filed:	October 12, 2000	Examiner:	Q. Li
For:	ADENO-ASSOCIATED VIRUS VECTORS ENCODING FACTOR VIII AND METHODS OF USING THE SAME		

June 12, 2002

Commissioner for Patents
Washington, DC 20231

SUBMITTAL OF FORMAL DRAWINGS
37 CFR § 1.85(c)

Sir:

In response to the requirement for new drawings as set forth in Paper No. 8 in the above application, there is enclosed herewith one set (25 sheets) of new formal drawings. It is requested that these new drawings be substituted for the originally filed drawings.

Respectfully submitted,

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Nora C. Martinez

Nora C. Martinez

FIG. 1A.


```
                10        20        30        40        50
      1234567890 1234567890 1234567890 1234567890 1234567890
TGGCCACTCC CTCTCTGCGC GCTCGCTCGC TCACTGAGGC CGGGCGACCA      50
AAGGTCGCCC GACGCCCGGG CTTTGCCCGG GCGGCCTCAG TGAGCGAGCG     100
AGCGCGCAGA GAGGGAGTGG CCAACTCCAT CACTAGGGGT TCCTCAGATC     150
TCTTTCTAAG TAAACAGTAC ATGAACCTTT ACCCCGTTGC TCGGCAACGG     200
CCTGGTCTGT GCCAAGTGTT TGCTGACGCA ACCCCCACTG GCTGGGGCTT     250
GGCCATAGGC CATCAGCGCA TGCGGATCTC AGTGTGGTTT TGCAAGAGGA     300
AGCAAAAAGC CTCTCCACCC AGGCCTGGAA TGTTTCCACC CAATGTCGAG     350
CAGTGTGGTT TTGCAAGAGG AAGCAAAAAG CCTCTCCACC CAGGCCTGGA     400
CTCGAGAGCT TCGACCACCA TGCAAATAGA GCTCTCCACC TGCTTCTTTC     450
                  M etGlnIleGl uLeuSerThr CysPhePheL
TGTGCCTTTT GCGATTCTGC TTTAGTGCCA CCAGAAGATA CTACCTGGGT     500
euCysLeuLe uArgPheCys PheSerAlaT hrArgArgTy rTyrLeuGly
GCAGTGGAAC TGTCATGGGA GTATATGCAA AGTGATCTCG GTGAGCTGCC     550
AlaValGluL euSerTrpAs pTyrMetGln SerAspLeuG lyGluLeuPr
TGTGGACGCA AGATTTCCTC CTAGAGTGCC AAAATCTTTT CCATTCAACA     600
oValAspAla ArgPheProP roArgValPr oLysSerPhe ProPheAsnT
CCTCAGTCGT GTACAAAAAG ACTCTGTTTG TAGAATTCAC GGTTCACCTT     650
hrSerValVa lTyrLysLys ThrLeuPheV alGluPheTh rValHisLeu
TTCAACATCG CTAAGCCAAG GCCACCCTGG ATGGGTCTGC TAGGTCCTAC     700
PheAsnIleA laLysProAr gProProTrp MetGlyLeuL euGlyProTh
CATCCAGGCT GAGGTTTATG ATACAGTGGT CATTACACTT AAGAACATGG     750
rIleGlnAla GluValTyrA spThrValVa lIleThrLeu LysAsnMetA
CTTCCCATCC TGTCAGTCTT CATGCTGTTG GTGTATCCTA CTGGAAAGCT     800
laSerHisPr oValSerLeu HisAlaValG lyValSerTy rTrpLysAla
TCTGAGGGAG CTGAATATGA TGATCAGACC AGTCAAAGGG AGAAAGAAGA     850
SerGluGlyA laGluTyrAs pAspGlnThr SerGlnArgG luLysGluAs
TGATAAAGTC TTCCCTGGTG CAAGCCATAC ATATGTCTGG CAGGTCCTGA     900
pAspLysVal PheProGlyG lySerHisTh rTyrValTrp GlnValLeuL
AAGAGAATGG TCCAATGGCC TCTGACCCAC TGTGCCTTAC CTACTCATAT     950
ysGluAsnGl yProMetAla SerAspProL euCysLeuTh rTyrSerTyr
```

FIG. 1B.

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
CTTTCTCATG	TGGACCTGGT	AAAAGACTTG	AATTCAGGCC	TCATTGGAGC	1000
LeuSerHisV	alAspLeuVa	lLysAspLeu	AsnSerGlyL	euIleGlyAl	
CCTACTAGTA	TGTAGAGAAG	GGAGTCTGGC	CAAGGAAAAG	ACACAGACCT	1050
aleuLeuVal	CysArgGluG	lySerLeuAl	aLysGluLys	ThrGlnThrL	
TGCACAAATT	TATACTACTT	TTTGCTGTAT	TTGATGAAGG	GAAAAGTTGG	1100
euHisLysPh	eIleLeuLeu	PheAlaValP	heAspGluGl	yLysSerTrp	
CACTCAGAAA	CAAAGAACTC	CTTGATGCAG	GATAGGGATG	CTGCATCTGC	1150
HisSerGluT	hrLysAsnSe	rLeuMetGln	AspArgAspA	laAlaSerAl	
TCGGGCCTGG	CCTAAAATGC	ACACAGTCAA	TGGTTATGTA	AACAGGTCTC	1200
aArgAlaTrp	ProLysMetH	isThrValAs	nGlyTyrVal	AsnArgSerL	
TGCCAGGTCT	GATTGGATGC	CACAGGAAAT	CAGTCTATTG	GCATGTGATT	1250
euProGlyLe	uIleGlyCys	HisArgLysS	erValTyrTr	pHisValIle	
GGAATGGGCA	CCACTCCTGA	AGTGCACTCA	ATATTCCTCG	AAGGTCACAC	1300
GlyMetGlyT	hrThrProGl	uValHisSer	IlePheLeuG	luGlyHisTh	
ATTTCTTGTG	AGGAACCATC	GCCAGGCGTC	CTTGGAAATC	TCGCCAATAA	1350
rPheLeuVal	ArgAsnHisA	rgGlnAlaSe	rLeuGluIle	SerProIleT	
CTTTCCTTAC	TGCTCAAACA	CTCTTGATGG	ACCTTGGACA	GTTTCTACTG	1400
hrPheLeuTh	rAlaGlnThr	LeuLeuMetA	spLeuGlyGl	nPheLeuLeu	
TTTTGTCATA	TCTCTTCCCA	CCAACATGAT	GGCATGGAAG	CTTATGTCAA	1450
PheCysHisI	leSerSerHi	sGlnHisAsp	GlyMetGluA	laTyrValLy	
AGTAGACAGC	TGTCCAGAGG	AACCCCAACT	ACGAATGAAA	AATAATGAAG	1500
sValAspSer	CysProGluG	luProGlnLe	uArgMetLys	AsnAsnGluG	
AAGCGGAAGA	CTATGATGAT	GATCTTACTG	ATTCTGAAAT	GGATGTGGTC	1550
luAlaGluAs	pTyrAspAsp	AspLeuThrA	spSerGluMe	tAspValVal	
AGGTTTGATG	ATGACAACTC	TCCTTCCTTT	ATCCAAATTC	GCTCAGTTGC	1600
ArgPheAspA	spAspAsnSe	rProSerPhe	IleGlnIleA	rgSerValAl	
CAAGAAGCAT	CCTAAAACTT	GGGTACATTA	CATTGCTGCT	GAAGAGGAGG	1650
aLysLysHis	ProLysThrT	rpValHisTy	rIleAlaAla	GluGluGluA	
ACTGGGACTA	TGCTCCCTTA	GTCCTCGCCC	CCGATGACAG	AAGTTATAAA	1700
spTrpAspTy	rAlaProLeu	ValLeuAlaP	roAspAspAr	gSerTyrLys	
AGTCAATATT	TGAACAATGG	CCCTCAGCGG	ATTGGTAGGA	AGTACAAAAA	1750
SerGlnTyrL	euAsnAsnGl	yProGlnArg	IleGlyArgL	ysTyrLysLy	
AGTCCGATTT	ATGGCATACA	CAGATGAAAC	CTTTAAGACT	CGTGAAGCTA	1800
sValArgPhe	MetAlaTyrT	hrAspGluTh	rPheLysThr	ArgGluAlaI	
TTCAGCATGA	ATCAGGAATC	TTGGGACCTT	TACTTTATGG	GGAAGTTGGA	1850
leGlnHisGl	uSerGlyIle	LeuGlyProL	euLeuTyrGl	yGluValGly	
GACACACTGT	TGATTATATT	TAAGAATCAA	GCAAGCAGAC	CATATAACAT	1900
AspThrLeuL	euIleIlePh	eLysAsnGln	AlaSerArgP	roTyrAsnIl	

FIG. 1C.


```
                10                  20                  30                  40                  50
      1234567890 1234567890 1234567890 1234567890 1234567890
CTACCCTCAC GGAATCACTG ATGTCCGTCC TTTGTATTCA AGGAGATTAC  1950
eTyrProHis GlyIleThrA spValArgPr oLeuTyrSer ArgArgLeuP
CAAAAGGTGT AAAACATTTG AAGGATTTTC CAATTCTGCC AGGAGAAATA  2000
roLysGlyVa lLysHisLeu LysAspPheP roIleLeuPr oGlyGluIle
TTCAAATATA AATGGACAGT GACTGTAGAA GATGGGCCAA CTAAATCAGA  2050
PheLysTyrL ysTrpThrVa lThrValGlu AspGlyProT hrLysSerAs
TCCTCGGTGC CTGACCCGCT ATTACTCTAG TTTCGTTAAT ATGGAGAGAG  2100
pProArgCys LeuThrArgT yrTyrSerSe rPheValAsn MetGluArgA
ATCTAGCTTC AGGACTCATT GGCCCTCTCC TCATCTGCTA CAAAGAATCT  2150
spLeuAlaSe rGlyLeuIle GlyProLeuL euIleCysTy rLysGluSer
GTAGATCAAA GAGGAAACCA GATAATGTCA GACAAGAGGA ATGTCATCCT  2200
ValAspGlnA rgGlyAsnGl nIleMetSer AspLysArgA snValIleLe
GTTTTCTGTA TTTGATGAGA ACCGAAGCTG GTACCTCACA GAGAATATAC  2250
uPheSerVal PheAspGluA snArgSerTr pTyrLeuThr GluAsnIleG
AACGCTTTCT CCCCAATCCA GCTGGAGTGC AGCTTGAGGA TCCAGAGTTC  2300
lnArgPheLe uProAsnPro AlaGlyValG lnLeuGluAs pProGluPhe
CAAGCCTCCA ACATCATGCA CAGCATCAAT GGCTATGTTT TTGATAGTTT  2350
GlnAlaSerA snIleMetHi sSerIleAsn GlyTyrValP heAspSerLe
GCAGTTGTCA GTTTGTTTGC ATGAGGTGGC ATACTGGTAC ATTCTAAGCA  2400
uGlnLeuSer ValCysLeuH isGluValAl aTyrTrpTyr IleLeuSerI
TTGGAGCACA GACTGACTTC CTTTCTGTCT TCTTCTCTGG ATATACCTTC  2450
leGlyAlaGl nThrAspPhe LeuSerValP hePheSerGl yTyrThrPhe
AAACACAAAA TGGTCTATGA AGACACACTC ACCCTATTCC CATTCTCAGG  2500
LysHisLysM etValTyrGl uAspThrLeu ThrLeuPheP roPheSerGl
AGAAACTGTC TTCATGTCGA TGGAAAACCC AGGTCTATGG ATTCTGGGGT  2550
yGluThrVal PheMetSerM etGluAsnPr oGlyLeuTrp IleLeuGlyC
GCCACAACTC AGACTTTCGG AACAGAGGCA TGACCGCCTT ACTGAAGGTT  2600
ysHisAsnSe rAspPheArg AsnArgGlyM etThrAlaLe uLeuLysVal
TCTAGTTGTG ACAAGAACAC TGGTGATTAT TACGAGGACA GTTATGAAGA  2650
SerSerCysA spLysAsnTh rGlyAspTyr TyrGluAspS erTyrGluAs
TATTTCAGCA TACTTGCTGA GTAAAAACAA TGCCATTGAA CCAAGAAGCT  2700
pIleSerAla TyrLeuLeuS erLysAsnAs nAlaIleGlu ProArgSerP
TCTCCCAGAA TTCAAGACAC CCTAGCACTA GGCAAAAGCA ATTTAATGCC  2750
heSerGlnAs nSerArgHis ProSerThrA rgGlnLysGl nPheAsnAla
ACCCCACCAG TCTTGAAACG CCATCAACGG GAAATAACTC GTACTACTCT  2800
ThrProProV alLeuLysAr gHisGlnArg GluIleThrA rgThrThrLe
TCAGTCAGAT CAAGAGGAAA TTGACTATGA TGATACCATA TCAGTTGAAA  2850
uGlnSerAsp GlnGluGluI leAspTyrAs pAspThrIle SerValGluM
```

FIG. 1D.


```
          10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
TGAAGAAGGA AGATTTTGAC ATTTATGATG AGGATGAAAA TCAGAGCCCC  2900
etLysLysGl uAspPheAsp IleTyrAspG luAspGluAs nGlnSerPro
CGCAGCTTTC AAAAGAAAAC ACGACACTAT TTTATTGCTG CAGTGGAGAG  2950
ArgSerPheG lnLysLysTh rArgHisTyr PheIleAlaA laValGluAr
GCTCTGGGAT TATGGGATGA GTAGCTCCCC ACATGTTCTA AGAAACAGGG  3000
gLeuTrpAsp TyrGlyMetS erSerSerPr oHisValLeu ArgAsnArgA
CTCAGAGTGG CAGTGTCCCT CAGTTCAAGA AAGTTGTTTT CCAGGAATTT  3050
laGlnSerGl ySerValPro GlnPheLysl ysValValPh eGlnGluPhe
ACTGATGGCT CCTTTACTCA GCCCTTATAC CGTGGAGAAC TAAATGAACA  3100
ThrAspGlyS erPheThrGl nProLeuTyr ArgGlyGluL euAsnGluHi
TTTGGGACTC CTGGGGCCAT ATATAAGAGC AGAAGTTGAA GATAATATCA  3150
sLeuGlyLeu LeuGlyProT yrIleArgAl aGluValGlu AspAsnIleM
TGGTAACTTT CAGAAATCAG GCCTCTCGTC CCTATTCCTT CTATTCTAGC  3200
etValThrPh eArgAsnGln AlaSerArgP roTyrSerPh eTyrSerSer
CTTATTTCTT ATGAGGAAGA TCAGAGGCAA GGAGCAGAAC CTAGAAAAAA  3250
LeuIleSerT yrGluGluAs pGlnArgGln GlyAlaGluP roArgLysAs
CTTTGTCAAG CCTAATGAAA CCAAAACTTA CTTTTGGAAA GTGCAACATC  3300
nPheValLys ProAsnGluT hrLysThrTy rPheTrpLys ValGlnHisH
ATATGGCACC CACTAAAGAT GAGTTTGACT GCAAAGCCTG GGCTTATTTC  3350
isMetAlaPr oThrLysAsp GluPheAspC ysLysAlaTr pAlaTyrPhe
TCTGATGTTG ACCTGGAAAA AGATGTGCAC TCAGGCCTGA TTGGACCCCT  3400
SerAspValA spLeuGluLy sAspValHis SerGlyLeuI leGlyProLe
TCTGGTCTGC CACACTAACA CACTGAACCC TGCTCATGGG AGACAAGTGA  3450
uLeuValCys HisThrAsnT hrLeuAsnPr oAlaHisGly ArgGlnValT
CAGTACAGGA ATTTGCTCTG TTTTTCACCA TCTTTGATGA GACCAAAAGC  3500
hrValGlnGl uPheAlaLeu PhePheThrI lePheAspGl uThrLysSer
TGGTACTTCA CTGAAAATAT GGAAAGAAAC TGCAGGGCTC CCTGCAATAT  3550
TrpTyrPheT hrGluAsnMe tGluArgAsn CysArgAlaP roCysAsnIl
CCAGATGGAA GATCCCACTT TTAAAGAGAA TTATCGCTTC CATGCAATCA  3600
eGlnMetGlu AspProThrP heLysGluAs nTyrArgPhe HisAlaIleA
ATGGCTACAT AATGGATACA CTACCTGGCT TAGTAATGGC TCAGGATCAA  3650
snGlyTyrIl eMetAspThr LeuProGlyL euValMetAl aGlnAspGln
AGGATTCGAT GGTATCTGCT CAGCATGGGC AGCAATGAAA ACATCCATTC  3700
ArgIleArgT rpTyrLeuLe uSerMetGly SerAsnGluA snIleHisSe
TATTCATTTC AGTGGACATG TGTTCACTGT ACGAAAAAAA GAGGAGTATA  3750
rIleHisPhe SerGlyHisV alPheThrVa lArgLysLys GluGluTyrL
AAATGGCACT GTACAATCTC TATCCAGGTG TTTTTGAGAC AGTGGAAATG  3800
ysMetAlaLe uTyrAsnLeu TyrProGlyV alPheGluTh rValGluMet
```

FIG. 1E.

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
TTACCATCCA	AAGCTGGAAT	TTGGCGGGTG	GAATGCCTTA	TTGGCGAGCA	3850
LeuProSerL	ysAlaGlyIl	eTrpArgVal	GluCysLeuI	leGlyGluHi	
TCTACATGCT	GGGATGAGCA	CACTTTTTCT	GGTGTACAGC	AATAAGTGTC	3900
sLeuHisAla	GlyMetSerT	hrLeuPheLe	uValTyrSer	AsnLysCysG	
AGACTCCCCT	GGGAATGGCT	TCTGGACACA	TTAGAGATTT	TCAGATTACA	3950
lnThrProLe	uGlyMetAla	SerGlyHisI	leArgAspPh	eGlnIleThr	
GCTTCAGGAC	AATATGGACA	GTGGGCCCCA	AAGCTGGCCA	GACTTCATTA	4000
AlaSerGlyG	lnTyrGlyGl	nTrpAlaPro	LysLeuAlaA	rgLeuHisTy	
TTCCGGATCA	ATCAATGCCT	GGAGCACCAA	GGAGCCCTTT	TCTTGGATCA	4050
rSerGlySer	IleAsnAlaT	rpSerThrLy	sGluProPhe	SerTrpIleL	
AGGTGGATCT	GTTGGCACCA	ATGATTATTC	ACGGCATCAA	GACCCAGGGT	4100
ysValAspLe	uLeuAlaPro	MetIleIleH	isGlyIleLy	sThrGlnGly	
GCCCGTCAGA	AGTTCTCCAG	CCTCTACATC	TCTCAGTTTA	TCATCATGTA	4150
AlaArgGlnL	ysPheSerSe	rLeuTyrIle	SerGlnPheI	leIleMetTy	
TAGTCTTGAT	GGGAAGAAGT	GGCAGACTTA	TCGAGGAAAT	TCCACTGGAA	4200
rSerLeuAsp	GlyLysLysT	rpGlnThrTy	rArgGlyAsn	SerThrGlyT	
CCTTAATGGT	CTTCTTTGGC	AATGTGGATT	CATCTGGGAT	AAAACACAAT	4250
hrLeuMetVa	lPhePheGly	AsnValAspS	erSerGlyIl	eLysHisAsn	
ATTTTTAACC	CTCCAATTAT	TGCTCGATAC	ATCCGTTTGC	ACCCAACTCA	4300
IlePheAsnP	roProIleIl	eAlaArgTyr	IleArgLeuH	isProThrHi	
TTATAGCATT	CGCAGCACTC	TTCGCATGGA	GTTGATGGGC	TGTGATTTAA	4350
sTyrSerIle	ArgSerThrL	euArgMetGl	uLeuMetGly	CysAspLeuA	
ATAGTTGCAG	CATGCCATTG	GGAATGGAGA	GTAAAGCAAT	ATCAGATGCA	4400
snSerCysSe	rMetProLeu	GlyMetGluS	erLysAlaIl	eSerAspAla	
CAGATTACTG	CTTCATCCTA	CTTTACCAAT	ATGTTTGCCA	CCTGGTCTCC	4450
GlnIleThrA	laSerSerTy	rPheThrAsn	MetPheAlaT	hrTrpSerPr	
TTCAAAAGCT	CGACTTCACC	TCCAAGGGAG	GAGTAATGCC	TGGAGACCTC	4500
oSerLysAla	ArgLeuHisL	euGlnGlyAr	gSerAsnAla	TrpArgProG	
AGGTGAATAA	TCCAAAAGAG	TGGCTGCAAG	TGGACTTCCA	GAAGACAATG	4550
lnValAsnAs	nProLysGlu	TrpLeuGlnV	alAspPheGl	nLysThrMet	
AAAGTCACAG	GAGTAACTAC	TCAGGGAGTA	AAATCTCTGC	TTACCAGCAT	4600
LysValThrG	lyValThrTh	rGlnGlyVal	LysSerLeuL	euThrSerMe	
GTATGTGAAG	GAGTTCCTCA	TCTCCAGCAG	TCAAGATGGC	CATCAGTGGA	4650
tTyrValLys	GluPheLeuI	leSerSerSe	rGlnAspGly	HisGlnTrpT	
CTCTCTTTTT	TCAGAATGGC	AAAGTAAAGG	TTTTTCAGGG	AAATCAAGAC	4700
hrLeuPhePh	eGlnAsnGly	LysValLysV	alPheGlnGl	yAsnGlnAsp	
TCCTTCACAC	CTGTGGTGAA	CTCTCTAGAC	CCACCGTTAC	TGACTCGCTA	4750
SerPheThrP	roValValAs	nSerLeuAsp	ProProLeuL	euThrArgTy	

FIG. 1F.


```
          10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
CCTTCGAATT CACCCCCAGA GTTGGGTGCA CCAGATTGCC CTGAGGATGG  4800
rLeuArgIle HisProGlnS erTrpValHi sGlnIleAla LeuArgMetG
AGGTTCTGGG CTGCGAGGCA CAGGACCTCT ACTGACTCGA GCGAGTTCTT  4850
luValLeuGl yCysGluAla GlnAspLeuT yr...
CTGAGGGGAT CGGCAATAAA AAGACAGAAT AAAACGCACG GGTGTTGGGT  4900

CGTTTGTTCG GATCCAGATC TAGGAACCCC TAGTGATGGA GTTGGCCACT  4950

CCCTCTCTGC GCGCTCGCTC GCTCACTGAG GCCGCCCGGG CAAAGCCCGG  5000

GCGTCGGGCG ACCTTTGGTC GCCCGGCCTC AGTGAGCGAG CGAGCGCGCA  5050

GAGAGGGAGT GGCCAACCCC CCCCCCCCCC CCCCTGCAGC CCAGCTGCAT  5100

TAATGAATCG GCCAACGCGC GGGGAGAGGC GGTTTGCGTA TTGGGCGCTC  5150

TTCCGCTTCC TCGCTCACTG ACTCGCTGCG CTCGGTCGTT CGGCTGCGGC  5200

GAGCGGTATC AGCTCACTCA AAGGCGGTAA TACGGTTATC CACAGAATCA  5250

GGGGATAACG CAGGAAAGAA CATGTGAGCA AAAGGCCAGC AAAAGGCCAG  5300

GAACCGTAAA AAGGCCGCGT TGCTGGCGTT TTTCCATAGG CTCCGCCCCC  5350

CTGACGAGCA TCACAAAAAT CGACGCTCAA GTCAGAGGTG GCGAAACCCG  5400

ACAGGACTAT AAAGATACCA GGCGTTTCCC CCTGGAAGCT CCCTCGTGCG  5450

CTCTCCTGTT CCGACCCTGC CGCTTACCGG ATACCTGTCC GCCTTTCTCC  5500

CTTCGGGAAG CGTGGCGCTT TCTCAATGCT CACGCTGTAG GTATCTCAGT  5550

TCGGTGTAGG TCGTTCGCTC CAAGCTGGGC TGTGTGCACG AACCCCCCGT  5600

TCAGCCCGAC CGCTGCGCCT TATCCGGTAA CTATCGTCTT GAGTCCAACC  5650

CGGTAAGACA CGACTTATCG CCACTGGCAG CAGCCACTGG TAACAGGATT  5700
```

FIG. 1G.


```
        10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
AGCAGAGCGA GGTATGTAGG CGGTGCTACA GAGTTCTTGA AGTGGTGGCC  5750

TAACTACGGC TACACTAGAA GGACAGTATT TGGTATCTGC GCTCTGCTGA  5800

AGCCAGTTAC CTTCGGAAAA AGAGTTGGTA GCTCTTGATC CGGCAAACAA  5850

ACCACCGCTG GTAGCGGTGG TTTTTTTGTT TGCAAGCAGC AGATTACGCG  5900

CAGAAAAAAA GGATCTCAAG AAGATCCTTT GATCTTTTCT ACGGGGTCTG  5950

ACGCTCAGTG GAACGAAAAC TCACGTTAAG GGATTTTGGT CATGAGATTA  6000

TCAAAAAGGA TCTTCACCTA GATCCTTTTA AATTAAAAAT GAAGTTTTAA  6050

ATCAATCTAA AGTATATATG AGTAAACTTG GTCTGACAGT TACCAATGCT  6100
                                                  ylGelIreS
TAATCAGTGA GGCACCTATC TCAGCGATCT GTCTATTTCG TTCATCCATA  6150
ueL...siHo rPlaV...gr AueLreSgrA psAelIulGn sAteMprTue
GTTGCCTGAC TCCCCGTCGT GTAGATAACT ACGATACGGG AGGGCTTACC  6200
LnlGgrAlaV ylGgrAgrAr hTreSueL.. .reSlaVorP orPreSlaVt
ATCTGGCCCC AGTGCTGCAA TGATACCGCG AGACCCACGC TCACCGGCTC  6250
eMnlGylGpr TsiHnlGueL reSlaValAu eLylGlaVre SlaVorPulG
CAGATTTATC AGCAATAAAC CAGCCAGCCG GAAGGGCCGA GCGCAGAAGT  6300
ueLnsAelIu eLueLueLyl GalAueLgrA ehPorPgrAa lAsyCehPsi
GGTCCTGCAA CTTTATCCGC CTCCATCCAG TCTATTAATT GTTGCCGGGA  6350
HpsAnlGueL syLelIgrAg rAprTylGrh T......nsA nsAylGorPu
AGCTAGAGTA AGTAGTTCGC CAGTTAATAG TTTGCGCAAC GTTGTTGCCA  6400
eL...ueLue LryInsAalA ueL...ryIn sAalAsyCgr AnlGnlGprT
TTGCTACAGG CATCGTGGTG TCACGCTCGT CGTTTGGTAT GGCTTCATTC  6450
nlG...ueLs yCgrAorPrh TlaVreSrhT rhTnlGryTo rPsyLteM..
AGCTCCGGTT CCCAACGATC AAGGCGAGTT ACATGATCCC CCATGTTGTG  6500
.reSgrAnsA ylGlaVelIu eLalAueL.. .teMelIylG prTrhTrhTs
CAAAAAAGCG GTTAGCTCCT TCGGTCCTCC GATCGTTGTC AGAAGTAAGT  6550
yCehPueLor P...reSgrA grApsAulGr eSgrAnlG.. .ehPryTrhT
TGGCCGCAGT GTTATCACTC ATGGTTATGG CAGCACTGCA TAATTCTCTT  6600
orPgrAueLr hTelIlaV.. .orP...orP ueLlaValAr yInsAulG..
ACTGTCATGC CATCCGTAAG ATGCTTTTCT GTGACTGGTG AGTACTCAAC  6650
.nlG...alA teMgrAueLe lIreSsyLnl GreSnlGsiH rhTreSueLp
```

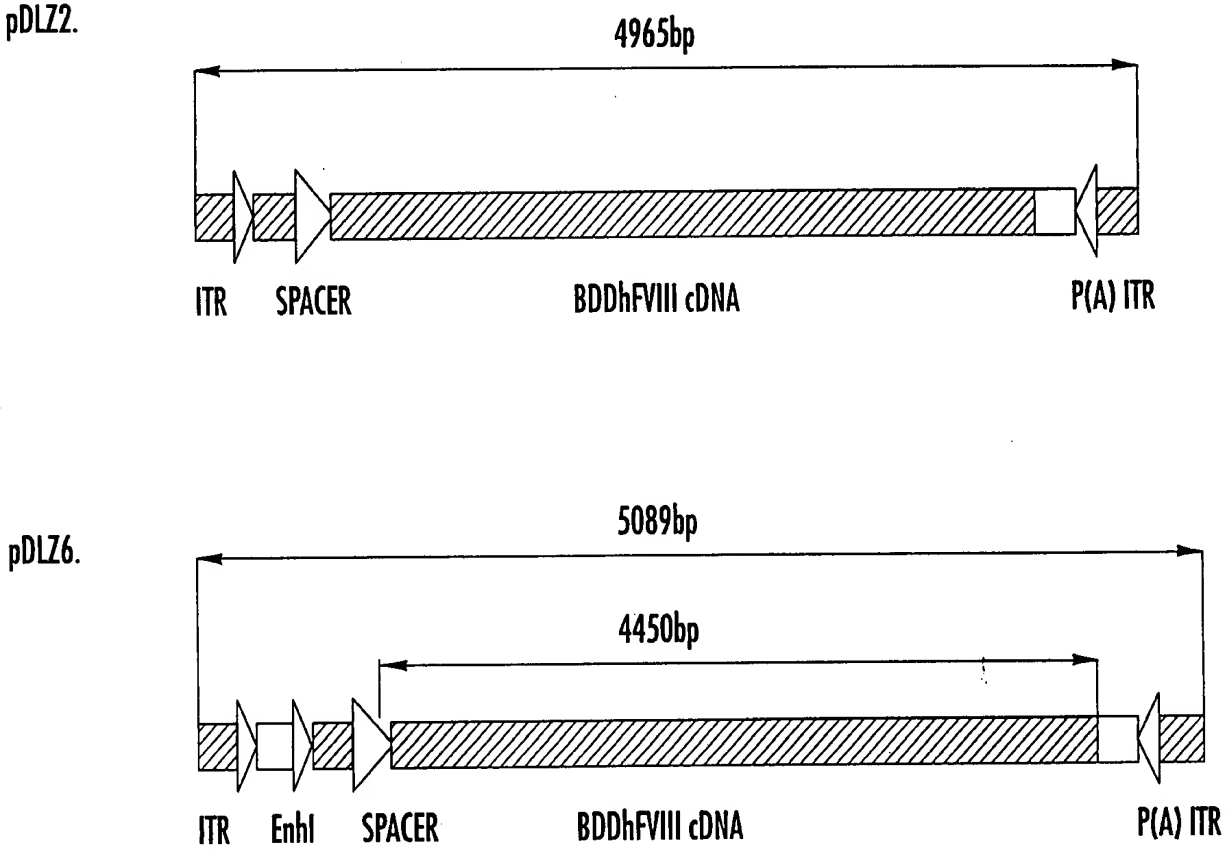
FIG. 1H.


```
          10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
CAAGTCATTC TGAGAATAGT GTATGCGGCG ACCGAGTTGC TCTTGCCCGG  6700
rTrhTteMgr AueLelIrhT ryTalAalAl aVreSnsAre SsyLylGorP
CGTCAATACG GGATAATACC GCGCCACATA GCAGAACTTT AAAAGTGCTC  6750
rhTueLlaVo rPryTryTgr AalAlaVryT syCehPsyLu eLueLalA..
ATCATTGGAA AACGTTCTTC GGGGCGAAAA CTCTCAAGGA TCTTACCGCT  6800
....nlGehP laVnsAsyLo rPalAehPla VgrAueLreS grAlaValAr
GTTGAGATCC AGTTCGATGT AACCCACTCG TGCACCCAAC TGATCTTCAG  6850
hTreSelIpr TnsAreSrhT laVprTulGs iHlaVprTre SelIsyLueL
CATCTTTTAC TTTCACCAGC GTTTCTGGGT GAGCAAAAAC AGGAAGGCAA  6900
teMsyL...s yL...prTgr AsyLnlGrhT ueLueLehPu eLehPalAeh
AATGCCGCAA AAAAGGGAAT AAGGGCGACA CGGAAATGTT GAATACTCAT  6950
PsiHgrAueL ehPorPehPu eLorPreSla VreSelInsA ehPlaV...l
ACTCTTCCTT TTTCAATATT ATTGAAGCAT TTATCAGGGT TATTGTCTCA  7000

TGAGCGGATA CATATTTGAA TGTATTTAGA AAAATAAACA AATAGGGGTT  7050

CCGCGCACAT TTCCCCGAAA AGTGCCACCT GACGTCTAAG AAACCATTAT  7100

TATCATGACA TTAACCTATA AAAATAGGCG TATCACGAGG CCCTTTCGTC  7150

TCGCGCGTTT CGGTGATGAC GGTGAAAACC TCTGACACAT GCAGCTCCCG  7200

GAGACGGTCA CAGCTTGTCT GTAAGCGGAT GCCGGGAGCA GACAAGCCCG  7250

TCAGGGCGCG TCAGCGGGTG TTGGCGGGTG TCGGGGCTGG CTTAACTATG  7300

CGGCATCAGA GCAGATTGTA CTGAGAGTGC ACCATATGCG GTGTGAAATA  7350

CCGCACAGAT GCGTAAGGAG AAAATACCGC ATCAGGAAAT TGTAAACGTT  7400

AATATTTTGT TAAAATTCGC GTTAAATTTT TGTTAAATCA GCTCATTTTT  7450

TAACCAATAG GCCGAAATCG GCAAAATCCC TTATAAATCA AAAGAATAGA  7500

CCGAGATAGG GTTGAGTGTT GTTCCAGTTT GGAACAAGAG TCCACTATTA  7550

AAGAACGTGG ACTCCAACGT CAAAGGGCGA AAAACCGTCT ATCAGGGCGA  7600
```

FIG. 1I.

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
TGGCCCACTA	CGTGAACCAT	CACCCTAATC	AAGTTTTTTG	GGGTCGAGGT	7650
GCCGTAAAGC	ACTAAATCGG	AACCCTAAAG	GGAGCCCCCG	ATTTAGAGCT	7700
TGACGGGGAA	AGCCGGCGAA	CGTGGCGAGA	AAGGAAGGGA	AGAAAGCGAA	7750
AGGAGCGGGC	GCTAGGGCGC	TGGCAAGTGT	AGCGGTCACG	CTGCGCGTAA	7800
CCACCACACC	CGCCGCGCTT	AATGCGCCGC	TACAGGGCGC	GTCGCGCCAT	7850
TCGCCATTCA	GGCTACGCAA	CTGTTGGGAA	GGGCGATCGG	TGCGGGCCTC	7900
TTCGCTATTA	CGCCAGCTGG	CTGCAGGGGG	GGGGGGGGGG	GGGT	7944

FIG. 2.


pDLZ2.
4965bp
ITR
SPACER
BDDhFVIII cDNA
P(A) ITR
pDLZ6.
5089bp
4450bp
ITR
EnhI
SPACER
BDDhFVIII cDNA
P(A) ITR

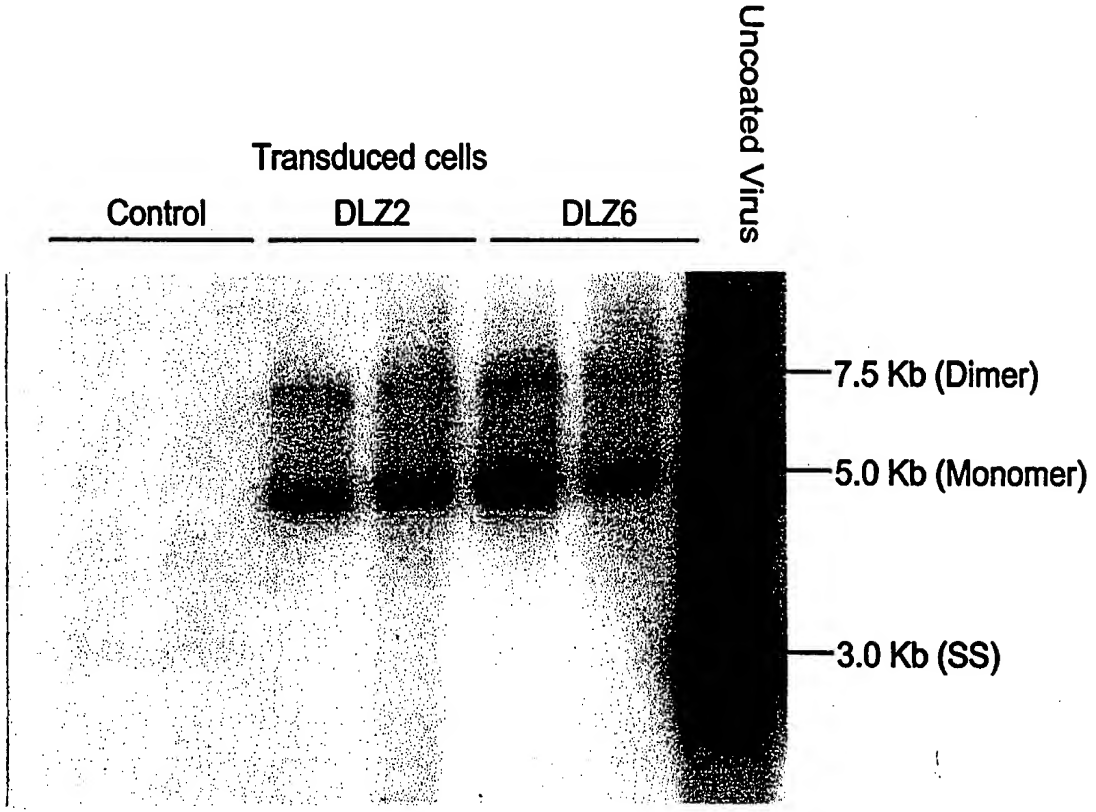
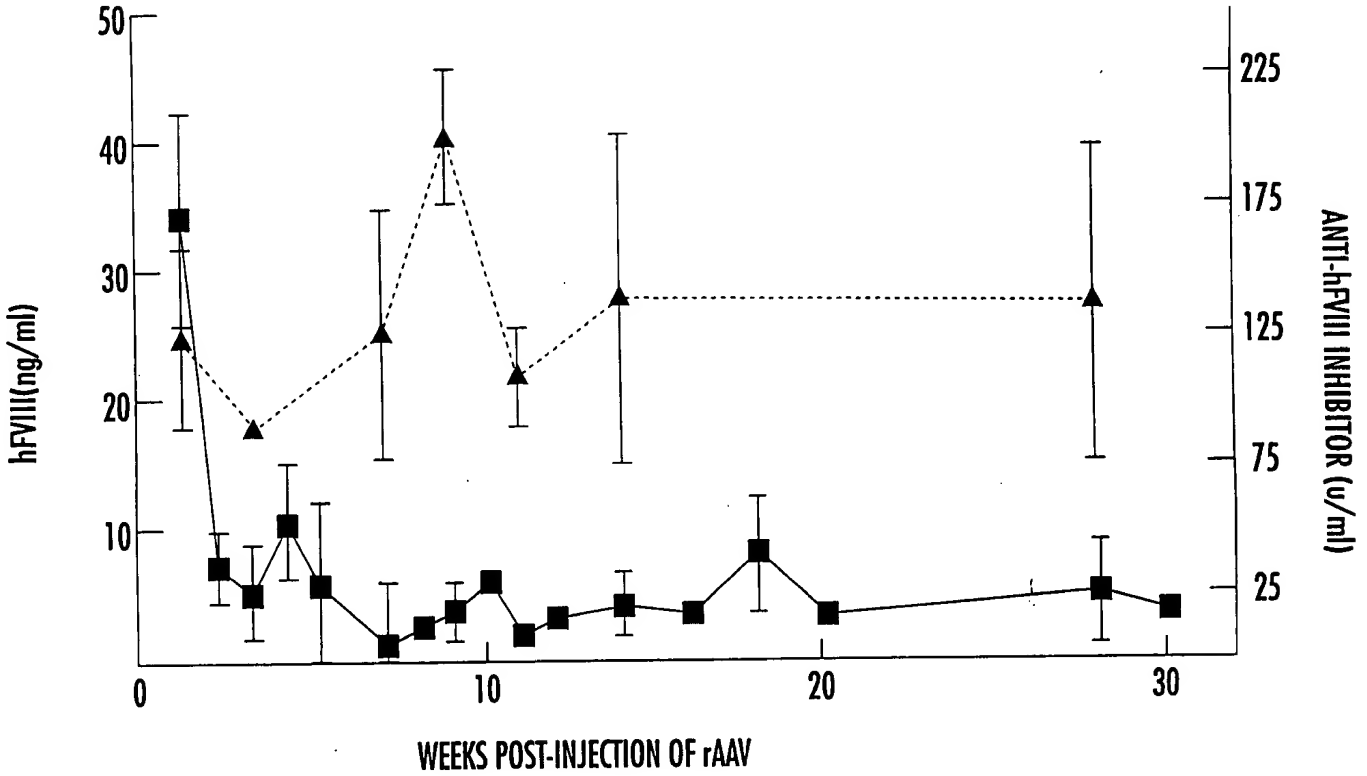

Transduced cells
Control
DLZ2
DLZ6
Uncoated Virus
7.5 Kb (Dimer)
5.0 Kb (Monomer)
3.0 Kb (SS)

FIG. 3.

FIG. 4.A.


50
40
30
20
10
0
10
20
30
225
175
125
75
25
hFVIII(ng/ml)
ANTI-hFVIII INHIBITOR (u/ml)
WEEKS POST-INJECTION OF rAAV

Title: Adeno-Associated Virus Vectors Encoding Factor VIII and Methods of Using the Same
Inventor(s): Walsh et al.
Application No: 09/689,430
Atty Dkt No: 35052/204373(5052-53)

FIG. 4.B.

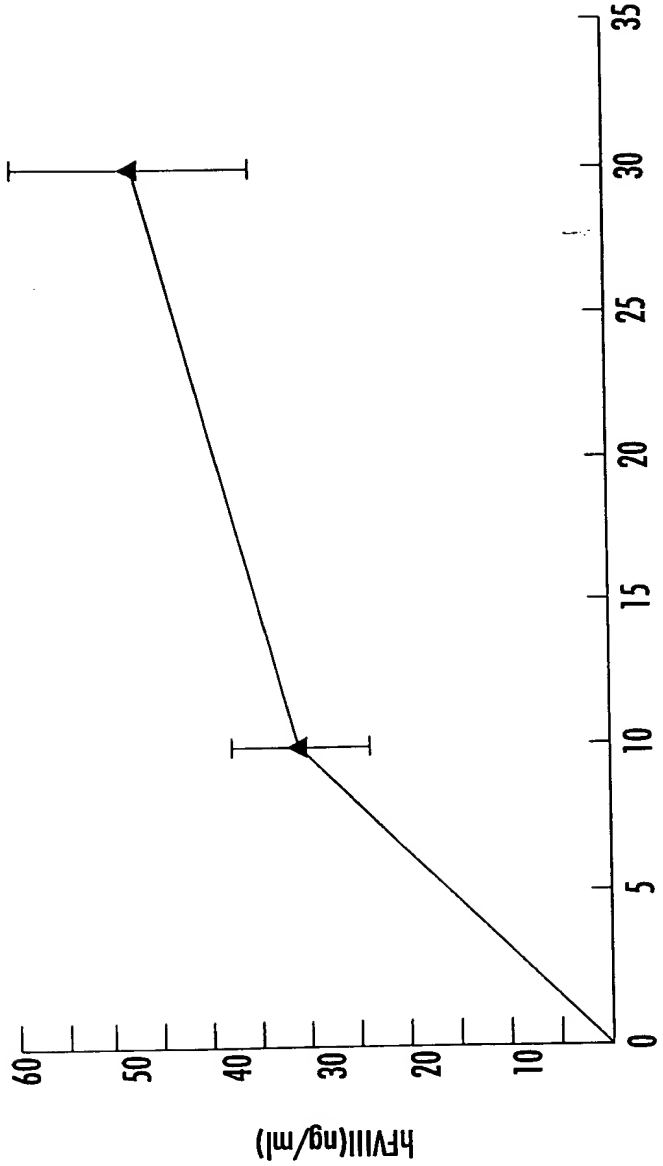


FIG. 5.A.

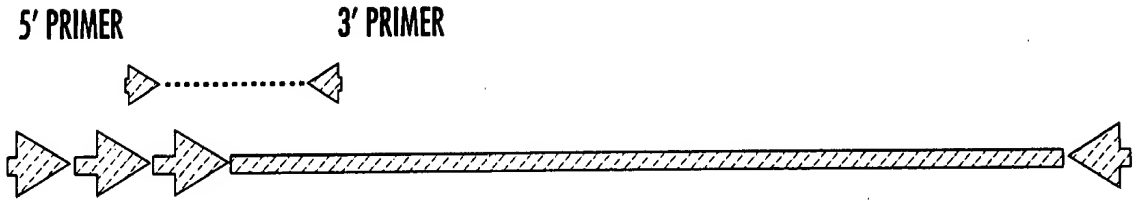

5' PRIMER
3' PRIMER

FIG. 5.B.

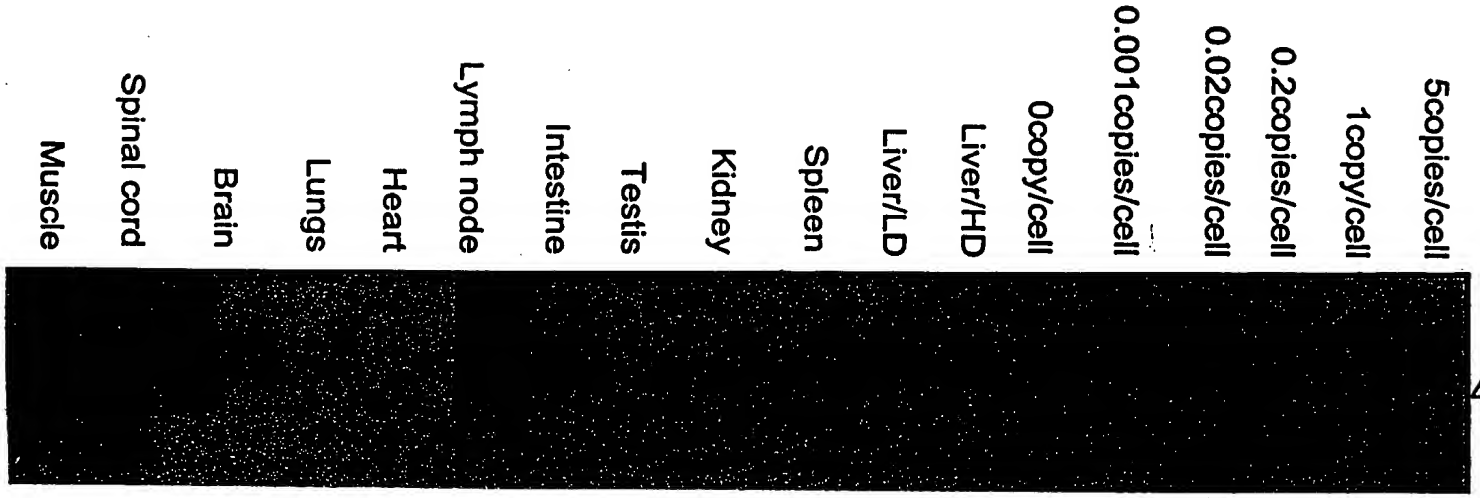

Muscle
Spinal cord
Brain
Lungs
Heart
Lymph node
Intestine
Testis
Kidney
Spleen
Liver/LD
Liver/HD
0copy/cell
0.001copies/cell
0.02copies/cell
0.2copies/cell
1copy/cell
5copies/cell
450 bp

FIG. 5.C.

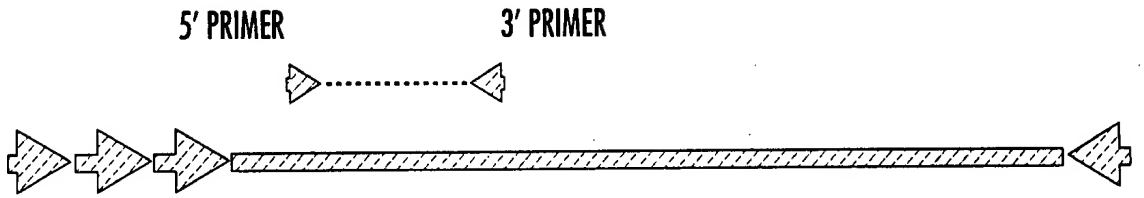

5' PRIMER
3' PRIMER

FIG. 5.D.

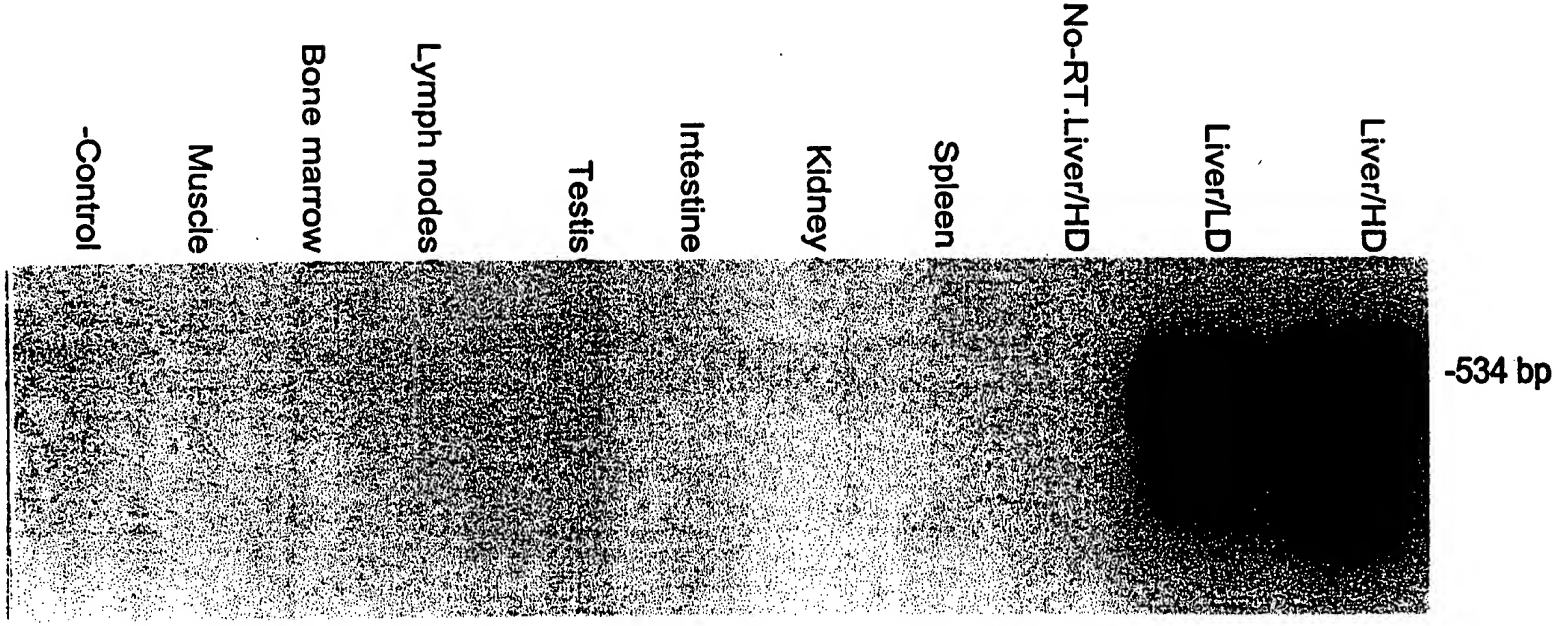

-Control
Muscle
Bone marrow
Lymph nodes
Testis
Intestine
Kidney
Spleen
No-RT.Liver/HD
Liver/LD
Liver/HD
-534 bp

FIG. 5.E.

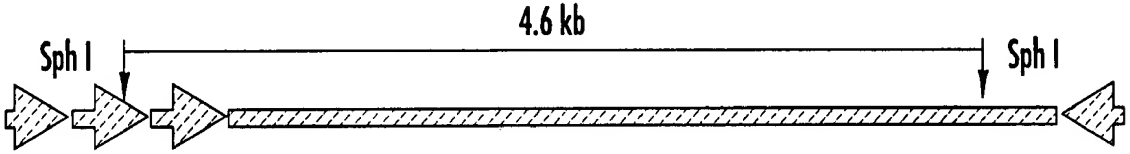

4.6 kb
Sph I
Sph I

FIG. 5.F.

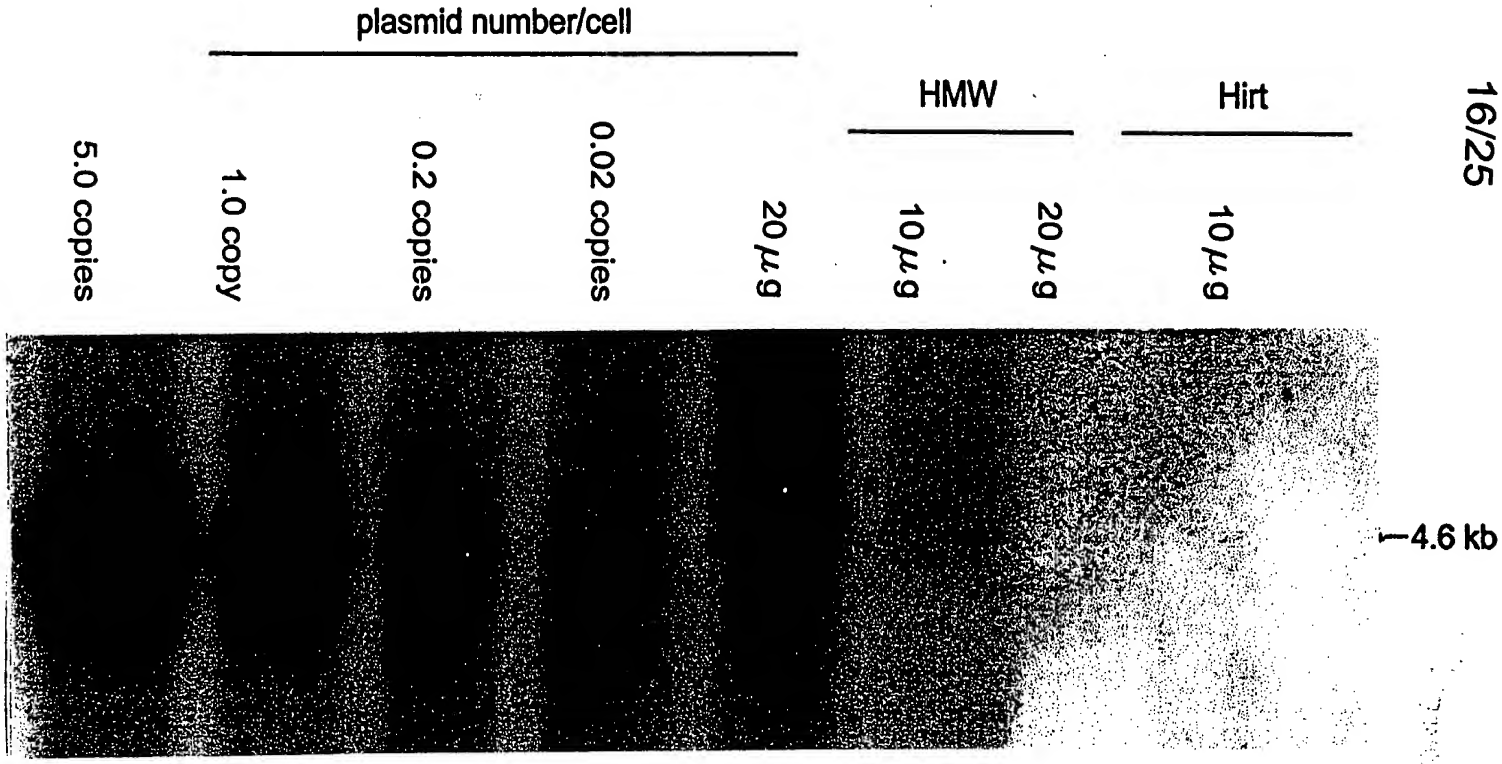

plasmid number/cell
HMW
Hirt
5.0 copies
1.0 copy
0.2 copies
0.02 copies
20 μg
10 μg
20 μg
10 μg
4.6 kb

FIG. 6.A.


```
          10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
TGGCCACTCC CTCTCTGCGC GCTCGCTCGC TCACTGAGGC CGGGCGACCA  50

AAGGTCGCCC GACGCCCGGG CTTTGCCCGG GCGGCCTCAG TGAGCGAGCG 100

AGCGCGCAGA GAGGGAGTGG CCAACTCCAT CACTAGGGGT TCCTCAGATC 150

TCTTTCTAAG TAAACAGTAC ATGAACCTTT ACCCCGTTGC TCGGCAACGG 200

CCTGGTCTGT GCCAAGTGTT TGCTGACGCA ACCCCCACTG GCTGGGGCTT 250

GGCCATAGGC CATCAGCGCA TGCGGATCTC AGTGTGGTTT TGCAAGAGGA 300

AGCAAAAAGC CTCTCCACCC AGGCCTGGAA TGTTTCCACC CAATGTCGAG 350

CAGTGTGGTT TTGCAAGAGG AAGCAAAAAG CCTCTCCACC CAGGCCTGGA 400

CTCGACCTCG AGAGTACTTC TAGAAATACG AGCCATGCAA GTAGAGCTCT 450
                                    MetGln ValGluLeuT
ACACCTGCTG CTTTCTGTGC CTTTTGCCCT TCAGCCTTAG TGCCACCAGA 500
yrThrCysCy sPheLeuCys LeuLeuProP heSerLeuSe rAlaThrArg
AAATACTACC TCGGTGCAGT GGAACTGTCC TGGGACTATA TGCAAAGTGA 550
LysTyrTyrL euGlyAlaVa lGluLeuSer TrpAspTyrM etGlnSerAs
CCTGCTCAGT GCGCTGCACG CGGATACAAG CTTTTCTTCC AGGGTGCCAG 600
pLeuLeuSer AlaLeuHisA laAspThrSe rPheSerSer ArgValProG
GATCTTTGCC ACTCACCACG TCAGTCACGT ACAGAAAGAC TGTGTTTGTA 650
lySerLeuPr oLeuThrThr SerValThrT yrArgLysTh rValPheVal
GAGTTTACAG ATGACCTTTT CAACATTGCC AAGCCCAGGC CACCGTGGAT 700
GluPheThrA spAspLeuPh eAsnIleAla LysProArgP roProTrpMe
GGGCCTGCTG GGTCCTACCA TCCAGGCTGA GGTTTATGAC ACAGTGGTCA 750
tGlyLeuLeu GlyProThrI leGlnAlaGl uValTyrAsp ThrValValI
TTGTCCTTAA GAACATGGCT TCTCATCCTG TCAGCCTTCA CGCTGTTGGT 800
leValLeuLy sAsnMetAla SerHisProV alSerLeuHi sAlaValGly
GTATCCTATT GGAAAGCTTC TGAAGGTGCT GAGTATGAGG ATCAGACCAG 850
ValSerTyrT rpLysAlaSe rGluGlyAla GluTyrGluA spGlnThrSe
CCAAAAGGAG AAGGAAGATG ATAATGTCAT TCCTGGTGAA AGCCATACCT 900
rGlnLysGlu LysGluAspA spAsnValIl eProGlyGlu SerHisThrT
ATGTCTGGCA GGTCCTGAAA GAGAATGGCC CAATGGCCTC TGATCCACCA 950
yrValTrpGl nValLeuLys GluAsnGlyP roMetAlaSe rAspProPro
```

FIG. 6.B.


```
        10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
TGTCTCACCT ACTCATATTT TTCACACGTG GACCTGGTGA AAGACCTGAA 1000
CysLeuThrT yrSerTyrPh eSerHisVal AspLeuValL ysAspLeuAs
TTCAGGCCTC ATTGGAGCCC TGCTGGTTTG CAAAGAAGGG AGTCTGGCCA 1050
nSerGlyLeu IleGlyAlaL euLeuValCy sLysGluGly SerLeuAlaL
AAGAAAGGAC ACAGACCTTG CAGGAATTTG TCCTACTTTT TGCTGTATTT 1100
ysGluArgTh rGlnThrLeu GlnGluPheV alLeuLeuPh eAlaValPhe
GATGAAGGGA AAAGTTGGCA CTCAGAAACA AATGCGTCTT TGACACAGGC 1150
AspGluGlyL ysSerTrpHi sSerGluThr AsnAlaSerL euThrGlnAl
TGAGGCCCAG CATGAGCTGC ACACCATCAA TGGCTATGTA AACAGGTCTC 1200
aGluAlaGln HisGluLeuH isThrIleAs nGlyTyrVal AsnArgSerL
TGCCAGGTCT TACTGTGTGT CACAAGAGAT CAGTCTATTG GCATGTGATT 1250
euProGlyLe uThrValCys HisLysArgS erValTyrTr pHisValIle
GGAATGGGCA CCACCCCCGA AGTGCACTCA ATTTTTCTCG AAGGTCACAC 1300
GlyMetGlyT hrThrProGl uValHisSer IlePheLeuG luGlyHisTh
ATTTCTTGTG AGGAACCACC GCCAGGCCTC CTTGGAGATC TCACCAATTA 1350
rPheLeuVal ArgAsnHisA rgGlnAlaSe rLeuGluIle SerProIleT
CTTTCCTTAC TGCTCAGACA TTCCTGATGG ACCTTGGCCA GTTTCTACTG 1400
hrPheLeuTh rAlaGlnThr PheLeuMetA spLeuGlyGl nPheLeuLeu
TTTTGTCATA TCCCTTCCCA TCAACATGAT GGTATGGAAG CTTATGTCAA 1450
PheCysHisI leProSerHi sGlnHisAsp GlyMetGluA laTyrValLy
AGTAGATAGC TGCCCAGAGG AACCCCAGCT GCGCATGAAA AATAATGAAG 1500
sValAspSer CysProGluG luProGlnLe uArgMetLys AsnAsnGluA
ATAAAGATTA TGATGATGGT CTTTATGATT CTGACATGGA CGTAGTTAGC 1550
spLysAspTy rAspAspGly LeuTyrAspS erAspMetAs pValValSer
TTTGATGACG ACAGCTCTTC TCCCTTTATC CAAATCCGCT CAGTTGCCAA 1600
PheAspAspA spSerSerSe rProPheIle GlnIleArgS erValAlaLy
GAAGCATCCT AAAACTTGGG TCCACTATAT TGCTGCTGAG GAGGAGGACT 1650
sLysHisPro LysThrTrpV alHisTyrIl eAlaAlaGlu GluGluAspT
GGGACTATGC TCCCTCAGGC CCCACCCCCA ATGATAGAAG TCATAAAAAT 1700
rpAspTyrAl aProSerGly ProThrProA snAspArgSe rHisLysAsn
CTGTATTTGA ACAATGGTCC TCAGCGGATT GGTAAGAAGT ACAAAAAAGT 1750
LeuTyrLeuA snAsnGlyPr oGlnArgIle GlyLysLysT yrLysLysVa
CCGATTTGTG GCATACACAG ATGAGACATT TAAGACTCGT GAAGCTATTC 1800
lArgPheVal AlaTyrThrA spGluThrPh eLysThrArg GluAlaIleG
AGTATGAATC AGGAATCCTG GGACCTTTAC TTTATGGAGA AGTTGGAGAC 1850
lnTyrGluSe rGlyIleLeu GlyProLeuL euTyrGlyGl uValGlyAsp
ACACTGCTGA TTATATTTAA GAATCAAGCC AGCCGGCCAT ATAACATCTA 1900
ThrLeuLeuI leIlePheLy sAsnGlnAla SerArgProT yrAsnIleTy
```

FIG. 6.C.


```
        10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
CCCTCATGGG ATCAATTATG TCACTCCTCT GCACACAGGG AGATTGCCAA 1950
rProHisGly IleAsnTyrV alThrProLe uHisThrGly ArgLeuProL
AAGGTGTGAA ACATTTGAAA GATATGCCAA TTCTGCCGGG AGAGATATTC 2000
ysGlyValLy sHisLeuLys AspMetProI leLeuProGl yGluIlePhe
AAGTATAAAT GGACAGTGAC CGTAGAAGAT GGACCAACTA AATCAGATCC 2050
LysTyrLysT rpThrValTh rValGluAsp GlyProThrL ysSerAspPr
TCGGTGCCTG ACCCGATATT ACTCAAGCTT CATTAATCTG GAGAGAGATC 2100
oArgCysLeu ThrArgTyrT yrSerSerPh eIleAsnLeu GluArgAspL
TAGCTTCAGG ACTCATTGGC CCTCTTCTCA TCTGCTACAA AGAATCTGTA 2150
euAlaSerGl yLeuIleGly ProLeuLeuI leCysTyrLy sGluSerVal
GATCAAAGAG GAAACCAGAT GATGTCAGAC AAGAGAAATG TCATCCTGTT 2200
AspGlnArgG lyAsnGlnMe tMetSerAsp LysArgAsnV alIleLeuPh
TTCTGTATTT GATGAGAATC GAAGCTGGTA CCTCACAGAG AATATGCAGC 2250
eSerValPhe AspGluAsnA rgSerTrpTy rLeuThrGlu AsnMetGlnA
GCTTCCTCCC CAATGCAGAT GTAGTGCAGC CCCATGACCC AGAGTTCCAA 2300
rgPheLeuPr oAsnAlaAsp ValValGlnP roHisAspPr oGluPheGln
CTCTCTAACA TCATGCACAG CATCAATGGC TATGTTTTTG ACAACTTGCA 2350
LeuSerAsnI leMetHisSe rIleAsnGly TyrValPheA spAsnLeuGl
GCTGTCAGTT TGTTTGCATG AGGTGGCGTA CTGGTACATT CTAAGTGTTG 2400
nLeuSerVal CysLeuHisG luValAlaTy rTrpTyrIle LeuSerValG
GAGCACAAAC TGACTTCCTG TCTGTCTTCT TCTCTGGATA TACCTTCAAA 2450
lyAlaGlnTh rAspPheLeu SerValPheP heSerGlyTy rThrPheLys
CACAAAATGG TCTATGAAGA CACACTTACC CTCTTCCCAT TCTCAGGAGA 2500
HisLysMetV alTyrGluAs pThrLeuThr LeuPheProP heSerGlyGl
AACTGTCTTC ATGTCAATGG AAAACCCAGG TCTGTGGGTT CTGGGGTGCC 2550
uThrValPhe MetSerMetG luAsnProGl yLeuTrpVal LeuGlyCysH
ACAACTCAGA CTTTCGGAAC AGAGGCATGA CAGCCTTACT GAAGGTTTCT 2600
isAsnSerAs pPheArgAsn ArgGlyMetT hrAlaLeuLe uLysValSer
AGTTGTAACA GGAACATTGA TGATTATTAT GAGGACACAT ACGAAGATAT 2650
SerCysAsnA rgAsnIleAs pAspTyrTyr GluAspThrT yrGluAspIl
TCCAACTCCC CTGCTAAATG AAAACAATGT AATTAAACCT AGAAGCTTCT 2700
eProThrPro LeuLeuAsnG luAsnAsnVa lIleLysPro ArgSerPheS
CCCAGAATTC AAGGCACCCT AGCACTAAGG AAAAGCAATT GAAAATGAAG 2750
erGlnAsnSe rArgHisPro SerThrLysG luLysGlnLe uLysMetLys
AGAGAAGATT TTGACATCTA CGGCGACTAT GAAAATCAGG GCCTCCGCAG 2800
ArgGluAspP heAspIleTy rGlyAspTyr GluAsnGlnG lyLeuArgSe
CTTTCAAAAG AAAACACGAC ACTATTTCAT TGCTGCAGTG GAGCGTCTCT 2850
rPheGlnLys LysThrArgH isTyrPheIl eAlaAlaVal GluArgLeuT
```

FIG. 6.D.


```
      10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
GGGATTATGG GATGAGTAGA TCTCCCCATA TACTAAGAAA CAGGGCTCAA  2900
rpAspTyrGl yMetSerArg SerProHisI leLeuArgAs nArgAlaGln
AGTGGGGATG TCCAGCAGTT CAAGAAGGTG GTTTTCCAGG AATTTACTGA  2950
SerGlyAspV alGlnGlnPh eLysLysVal ValPheGlnG luPheThrAs
TGGATCCTTT ACTCAGCCCT TATACCGTGG AGAACTGAAT GAACACTTGG  3000
pGlySerPhe ThrGlnProL euTyrArgGl yGluLeuAsn GluHisLeuG
GACTCTTGGG GCCATATATA AGAGCAGAAG TTGAAGACAA TATCGTGGTA  3050
lyLeuLeuGl yProTyrIle ArgAlaGluV alGluAspAs nIleValVal
ACTTTCAAAA ACCAGGCCTC TCGTCCCTAC TCCTTCTATT CTAGTCTTAT  3100
ThrPheLysA snGlnAlaSe rArgProTyr SerPheTyrS erSerLeuIl
TTCTTATGAC GAAGATGAGG GACAAGGAGC AGAACCTAGA AGAAAGTTTG  3150
eSerTyrAsp GluAspGluG lyGlnGlyAl aGluProArg ArgLysPheV
TCAACCCTAA TGAAACCAAA ATTTACTTTT GGAAAGTGCA GCATCATATG  3200
alAsnProAs nGluThrLys IleTyrPheT rpLysValGl nHisHisMet
GCACCCACTA AAGATGAGTT TGACTGCAAA GCCTGGGCTT ATTTTTCTGA  3250
AlaProThrL ysAspGluPh eAspCysLys AlaTrpAlaT yrPheSerAs
TGTTGATTTG GAGAAAGATG TGCACTCAGG CTTGATTGGA CCCCTTCTGA  3300
pValAspLeu GluLysAspV alHisSerGl yLeuIleGly ProLeuLeuI
TCTGCCGCAG TAACACACTG AACCCTGCTC ATGGGAGACA AGTGACAGTG  3350
leCysArgSe rAsnThrLeu AsnProAlaH isGlyArgGl nValThrVal
CAGGAGTTTG CCCTGGTTTT CACTATATTC GATGAGACTA AGAGCTGGTA  3400
GlnGluPheA laLeuValPh eThrIlePhe AspGluThrL ysSerTrpTy
CTTCACTGAA AACCTGGAAA GGAACTGTAG AGCTCCCTGC AATGTCCAGA  3450
rPheThrGlu AsnLeuGluA rgAsnCysAr gAlaProCys AsnValGlnL
AGGAGGACCC TACTCTAAAA GAAAACTTCC GCTTCCATGC AATCAACGGC  3500
ysGluAspPr oThrLeuLys GluAsnPheA rgPheHisAl aIleAsnGly
TATGTGAAGG ATACACTCCC TGGCTTAGTA ATGGCTCAGG ATCAAAAGGT  3550
TyrValLysA spThrLeuPr oGlyLeuVal MetAlaGlnA spGlnLysVa
TCGATGGTAT CTGCTCAGCA TGGGCAGCAA CGAAAACATT CATTCCATTC  3600
lArgTrpTyr LeuLeuSerM etGlySerAs nGluAsnIle HisSerIleH
ACTTCAGTGG ACATGTGTTC ACTGTACGGA AAAAAGAGGA ATATAAAATG  3650
isPheSerGl yHisValPhe ThrValArgL ysLysGluGl uTyrLysMet
GCAGTCTACA ACCTCTATCC AGGTGTTTTT GAGACTGTGG AAATGCTACC  3700
AlaValTyrA snLeuTyrPr oGlyValPhe GluThrValG luMetLeuPr
ATCCCAAGTT GGAATCTGGC GGATAGAATG CCTTATCGGC GAGCACCTGC  3750
oSerGlnVal GlyIleTrpA rgIleGluCy sLeuIleGly GluHisLeuG
AAGCCGGGAT GAGCACTCTG TTTCTGGTGT ACAGCAAGAA GTGTCAGACT  3800
lnAlaGlyMe tSerThrLeu PheLeuValT yrSerLysLy sCysGlnThr
```

FIG. 6.E.


```
        10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
CCACTGGGGA TGGCTTCCGG ACACATTAGA GATTTTCAGA TTACAGCTTC  3850
ProLeuGlyM etAlaSerGl yHisIleArg AspPheGlnI leThrAlaSe
AGGACAATAT GGACAGTGGG CCCCAAAGCT GGCCAGACTT CATTATTCCG  3900
rGlyGlnTyr GlyGlnTrpA laProLysLe uAlaArgLeu HisTyrSerG
GATCAATCAA TGCCTGGAGC ACCAAGGATC CCTTTTCCTG GATCAAGGTG  3950
lySerIleAs nAlaTrpSer ThrLysAspP roPheSerTr pIleLysVal
GATCTCTTGG CACCGATGAT TATTCACGGC ATCATGACCC AGGGGGCCCG  4000
AspLeuLeuA laProMetIl eIleHisGly IleMetThrG lnGlyAlaAr
CCAGAAGTTC TCCAGCCTCT ACGTGTCTCA GTTTATCATC ATGTACAGTC  4050
gGlnLysPhe SerSerLeuT yrValSerGl nPheIleIle MetTyrSerL
TGGATGGCAA CAAGTGGCAC AGTTACCGAG GGAATTCCAC GGGGACCTTA  4100
euAspGlyAs nLysTrpHis SerTyrArgG lyAsnSerTh rGlyThrLeu
ATGGTCTTCT TTGGCAACGT GGATTCATCT GGGATCAAAC ACAATATTTT  4150
MetValPheP heGlyAsnVa lAspSerSer GlyIleLysH isAsnIlePh
TAACCCTCCG ATTATTGCTC AGTACATCCG TTTGCACCCA ACCCATTACA  4200
eAsnProPro IleIleAlaG lnTyrIleAr gLeuHisPro ThrHisTyrS
GCATCCGCAG CACTCTTCGC ATGGAGCTCT TGGGCTGTGA CTTCAACAGT  4250
erIleArgSe rThrLeuArg MetGluLeuL euGlyCysAs pPheAsnSer
TGCAGCATGC CGCTGGGGAT GGAGAGTAAA GCAATATCAG ATGCTCAGAT  4300
CysSerMetP roLeuGlyMe tGluSerLys AlaIleSerA spAlaGlnIl
CACTGCCTCG TCCTACCTAA GCAGTATGCT TGCCACTTGG TCTCCTTCCC  4350
eThrAlaSer SerTyrLeuS erSerMetLe uAlaThrTrp SerProSerG
AAGCCCGGCT GCACCTGCAG GGCAGGACTA ATGCCTGGAG ACCTCAGGCA  4400
lnAlaArgLe uHisLeuGln GlyArgThrA snAlaTrpAr gProGlnAla
AATAACCCAA AAGAGTGGCT GCAAGTGGAC TTCCGGAAGA CCATGAAAGT  4450
AsnAsnProL ysGluTrpLe uGlnValAsp PheArgLysT hrMetLysVa
CACAGGAATA ACCACCCAGG GGGTGAAATC TCTCCTCATC AGCATGTATG  4500
lThrGlyIle ThrThrGlnG lyValLysSe rLeuLeuIle SerMetTyrV
TGAAGGAGTT CCTCATCTCC AGTAGTCAAG ATGGCCATAA CTGGACTCTG  4550
alLysGluPh eLeuIleSer SerSerGlnA spGlyHisAs nTrpThrLeu
TTTCTTCAGA ATGGCAAAGT CAAGGTCTTC CAGGGAAACC GGGACTCCTC  4600
PheLeuGlnA snGlyLysVa lLysValPhe GlnGlyAsnA rgAspSerSe
CACGCCTGTG CGGAACCGTC TCGAACCCCC GCTGGTGGCT CGCTACGTGC  4650
rThrProVal ArgAsnArgL euGluProPr oLeuValAla ArgTyrValA
GCCTGCACCC GCAGAGCTGG GCGCACCACA TCGCCCTGAG GCTGGAGGTC  4700
rgLeuHisPr oGlnSerTrp AlaHisHisI leAlaLeuAr gLeuGluVal
CTGGGCTGCG ACACCCAGCA GCCCGCCTGA CCCGCGCCTC TGCGGCCCTG  4750
LeuGlyCysA spThrGlnGl nProAla...
```

FIG. 6.F.

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
TCTCCCCTGC	CTCCCTGCCC	TGTCCCCGCG	GCTTCCCATC	AAGCTTATCG	4800
ATACCGTCGA	GCGAGTTCTT	CTGAGGGGAT	CGGCAATAAA	AAGACAGAAT	4850
AAAACGCACG	GGTGTTGGGT	CGTTTGTTCG	GATCCAGATC	TAGGAACCCC	4900
TAGTGATGGA	GTTGGCCACT	CCCTCTCTGC	GCGCTCGCTC	GCTCACTGAG	4950
GCCGCCCGGG	CAAAGCCCGG	GCGTCGGGCG	ACCTTTGGTC	GCCCGGCCTC	5000
AGTGAGCGAG	CGAGCGCGCA	GAGAGGGAGT	GGCCAACCCC	CCCCCCCCCC	5050
CCCCTGCAGC	CCAGCTGCAT	TAATGAATCG	GCCAACGCGC	GGGGAGAGGC	5100
GGTTTGCGTA	TTGGGCGCTC	TTCCGCTTCC	TCGCTCACTG	ACTCGCTGCG	5150
CTCGGTCGTT	CGGCTGCGGC	GAGCGGTATC	AGCTCACTCA	AAGGCGGTAA	5200
TACGGTTATC	CACAGAATCA	GGGGATAACG	CAGGAAAGAA	CATGTGAGCA	5250
AAAGGCCAGC	AAAAGGCCAG	GAACCGTAAA	AAGGCCGCGT	TGCTGGCGTT	5300
TTTCCATAGG	CTCCGCCCCC	CTGACGAGCA	TCACAAAAAT	CGACGCTCAA	5350
GTCAGAGGTG	GCGAAACCCG	ACAGGACTAT	AAAGATACCA	GGCGTTTCCC	5400
CCTGGAAGCT	CCCTCGTGCG	CTCTCCTGTT	CCGACCCTGC	CGCTTACCGG	5450
ATACCTGTCC	GCCTTTCTCC	CTTCGGGAAG	CGTGGCGCTT	TCTCAATGCT	5500
CACGCTGTAG	GTATCTCAGT	TCGGTGTAGG	TCGTTCGCTC	CAAGCTGGGC	5550
TGTGTGCACG	AACCCCCCGT	TCAGCCCGAC	CGCTGCGCCT	TATCCGGTAA	5600
CTATCGTCTT	GAGTCCAACC	CGGTAAGACA	CGACTTATCG	CCACTGGCAG	5650
CAGCCACTGG	TAACAGGATT	AGCAGAGCGA	GGTATGTAGG	CGGTGCTACA	5700

FIG. 6.G.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        10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
GAGTTCTTGA AGTGGTGGCC TAACTACGGC TACACTAGAA GGACAGTATT  5750

TGGTATCTGC GCTCTGCTGA AGCCAGTTAC CTTCGGAAAA AGAGTTGGTA  5800

GCTCTTGATC CGGCAAACAA ACCACCGCTG GTAGCGGTGG TTTTTTTGTT  5850

TGCAAGCAGC AGATTACGCG CAGAAAAAAA GGATCTCAAG AAGATCCTTT  5900

GATCTTTTCT ACGGGGTCTG ACGCTCAGTG GAACGAAAAC TCACGTTAAG  5950

GGATTTTGGT CATGAGATTA TCAAAAAGGA TCTTCACCTA GATCCTTTTA  6000

AATTAAAAAT GAAGTTTTAA ATCAATCTAA AGTATATATG AGTAAACTTG  6050

GTCTGACAGT TACCAATGCT TAATCAGTGA GGCACCTATC TCAGCGATCT  6100
          ylGelIreS ueL...siHo rPlaV...gr AueLreSgrA
GTCTATTTCG TTCATCCATA GTTGCCTGAC TCCCCGTCGT GTAGATAACT  6150
psAelIulGn sAteMprTue LnlGgrAlaV ylGgrAgrAr hTreSueL..
ACGATACGGG AGGGCTTACC ATCTGGCCCC AGTGCTGCAA TGATACCGCG  6200
.reSlaVorP orPreSlaVt eMnlGylGpr TsiHnlGueL reSlaValAu
AGACCCACGC TCACCGGCTC CAGATTTATC AGCAATAAAC CAGCCAGCCG  6250
eLylGlaVre SlaVorPulG ueLnsAelIu eLueLueLyl GalAueLgrA
GAAGGGCCGA GCGCAGAAGT GGTCCTGCAA CTTTATCCGC CTCCATCCAG  6300
ehPorPgrAa lAsyCehPsi HpsAnlGueL syLelIgrAg rAprTylGrh
TCTATTAATT GTTGCCGGGA AGCTAGAGTA AGTAGTTCGC CAGTTAATAG  6350
T......nsA nsAylGorPu eL...ueLue LryTnsAalA ueL...ryTn
TTTGCGCAAC GTTGTTGCCA TTGCTACAGG CATCGTGGTG TCACGCTCGT  6400
sAalAsyCgr AnlGnlGprT nlG...ueLs yCgrAorPrh TlaVreSrhT
CGTTTGGTAT GGCTTCATTC AGCTCCGGTT CCCAACGATC AAGGCGAGTT  6450
rhTnlGryTo rPsyLteM.. .reSgrAnsA ylGlaVelIu eLalAueL..
ACATGATCCC CCATGTTGTG CAAAAAAGCG GTTAGCTCCT TCGGTCCTCC  6500
.teMelIylG prTrhTrhTs yCehPueLor P...reSgrA grApsAulGr
GATCGTTGTC AGAAGTAAGT TGGCCGCAGT GTTATCACTC ATGGTTATGG  6550
eSgrAnlG.. .ehPryTrhT orPgrAueLr hTelIlaV.. .orP...orP
CAGCACTGCA TAATTCTCTT ACTGTCATGC CATCCGTAAG ATGCTTTTCT  6600
ueLlaValAr yTnsAulG.. .nlG...alA teMgrAueLe lIreSsyLnl
GTGACTGGTG AGTACTCAAC CAAGTCATTC TGAGAATAGT GTATGCGGCG  6650
GreSnlGsiH rhTreSueLp rTrhTteMgr AueLelIrhT ryTalAalAl
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FIG. 6.H.

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
ACCGAGTTGC	TCTTGCCCGG	CGTCAATACG	GGATAATACC	GCGCCACATA	6700
aVreSnsAre	SsyLylGorP	rhTueLlaVo	rPryTryTgr	AalAlaVryT	
GCAGAACTTT	AAAAGTGCTC	ATCATTGGAA	AACGTTCTTC	GGGGCGAAAA	6750
syCehPsyLu	eLueLalA..	....nlGehP	laVnsAsyLo	rPalAehPla	
CTCTCAAGGA	TCTTACCGCT	GTTGAGATCC	AGTTCGATGT	AACCCACTCG	6800
VgrAueLreS	grAlaValAr	hTreSelIpr	TnsAreSrhT	laVprTulGs	
TGCACCCAAC	TGATCTTCAG	CATCTTTTAC	TTTCACCAGC	GTTTCTGGGT	6850
iHlaVprTre	SelIsyLueL	teMsyL...s	yL...prTgr	AsyLnlGrhT	
GAGCAAAAAC	AGGAAGGCAA	AATGCCGCAA	AAAAGGGAAT	AAGGGCGACA	6900
ueLueLehPu	eLehPalAeh	PsiHgrAueL	ehPorPehPu	eLorPreSla	
CGGAAATGTT	GAATACTCAT	ACTCTTCCTT	TTTCAATATT	ATTGAAGCAT	6950
VreSelInsA	ehPlaV...l				
TTATCAGGGT	TATTGTCTCA	TGAGCGGATA	CATATTTGAA	TGTATTTAGA	7000
AAAATAAACA	AATAGGGGTT	CCGCGCACAT	TTCCCCGAAA	AGTGCCACCT	7050
GACGTCTAAG	AAACCATTAT	TATCATGACA	TTAACCTATA	AAAATAGGCG	7100
TATCACGAGG	CCCTTTCGTC	TCGCGCGTTT	CGGTGATGAC	GGTGAAAACC	7150
TCTGACACAT	GCAGCTCCCG	GAGACGGTCA	CAGCTTGTCT	GTAAGCGGAT	7200
GCCGGGAGCA	GACAAGCCCG	TCAGGGCGCG	TCAGCGGGTG	TTGGCGGGTG	7250
TCGGGGCTGG	CTTAACTATG	CGGCATCAGA	GCAGATTGTA	CTGAGAGTGC	7300
ACCATATGCG	GTGTGAAATA	CCGCACAGAT	GCGTAAGGAG	AAAATACCGC	7350
ATCAGGAAAT	TGTAAACGTT	AATATTTTGT	TAAAATTCGC	GTTAAATTTT	7400
TGTTAAATCA	GCTCATTTTT	TAACCAATAG	GCCGAAATCG	GCAAAATCCC	7450
TTATAAATCA	AAAGAATAGA	CCGAGATAGG	GTTGAGTGTT	GTTCCAGTTT	7500
GGAACAAGAG	TCCACTATTA	AAGAACGTGG	ACTCCAACGT	CAAAGGGCGA	7550
AAAACCGTCT	ATCAGGGCGA	TGGCCCACTA	CGTGAACCAT	CACCCTAATC	7600

FIG. 6.I.

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
AAGTTTTTTG	GGGTCGAGGT	GCCGTAAAGC	ACTAAATCGG	AACCCTAAAG	7650
GGAGCCCCCG	ATTTAGAGCT	TGACGGGGAA	AGCCGGCGAA	CGTGGCGAGA	7700
AAGGAAGGGA	AGAAAGCGAA	AGGAGCGGGC	GCTAGGGCGC	TGGCAAGTGT	7750
AGCGGTCACG	CTGCGCGTAA	CCACCACACC	CGCCGCGCTT	AATGCGCCGC	7800
TACAGGGCGC	GTCGCGCCAT	TCGCCATTCA	GGCTACGCAA	CTGTTGGGAA	7850
GGGCGATCGG	TGCGGGCCTC	TTCGCTATTA	CGCCAGCTGG	CTGCAGGGGG	7900
GGGGGGGGGG	GGGT				7914